(ii) contacting a T cell, which has been stimulated *via* its T cell receptor, with a candidate substance under conditions that would permit a sustained rise in intracellular Ca^{2+} levels in the absence of the substance, and determining whether the substance inhibits a sustained rise in intracellular Ca^{2+} levels.

30. A method according to claim 29 employing the cyclase assay of alternative (i).

31. A method according to claim 29 employing the Ca^{2+} level determination of alternative (ii).

Remarks

This is a national phase entry of the PCT/GB99/04295 application referenced above. A "Cross-References to Related Applications" section and Abstract were added to the specification. The abstract and related application data are identical to what is presented on the front of the published version of the PCT application (WO 00/37089 dated 29 June 2000). No new matter is presented.

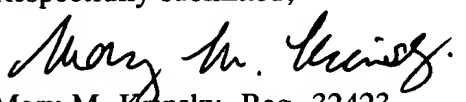
The pending PCT 18 claims were amended to provide a claim set that conforms to U.S. practice and eliminates multiple dependent claims to save fees. Claims 1 to 5, 8 and 15 were amended as indicated in the marked up version set out below. The rest of the claims were cancelled and replaced by new claims 19 to 31. Because the final set has 20 claims total, 3 of which are independent, no additional claim fees are due or presented herewith.

New claim 19 particularly points out specific compounds used in some embodiments described in the specification on page 11 at lines 6 to 7. New claim 20 particularly points out a couple of groups of compounds used in embodiments set out in the specification on page 11 at lines 10 to 22. New claim 8 directed to immune response modulation in mammals is supported in the specification on page 5 at lines 21 to 22.

New claim 22 directed to *ex vivo* therapy is supported in the specification on page 16 at lines 20 to 21. New claim 23 is a rewritten version of originally presented claim 1 supported in the specification on page 16 at lines 16 to 24. Claims 24 to 26 track the language of originally presented claims 2 to 4. New claim 27 combines the limitations of originally presented claims 11 to 13. New claim 30 particularly points out an embodiment set out in former claim 11, and new claim 31 is directed to the embodiment originally presented in claim 13. No new matter is presented.

If the undersigned can assist in the prosecution of this application in any way, please call at the number below.

Respectfully submitted,



Mary M. Krinsky, Reg. 32423
79 Trumbull St., New Haven, CT 06511
203-773-9544

Marked-Up Copy of Amendments Required by 37 C.F.R. 1.121

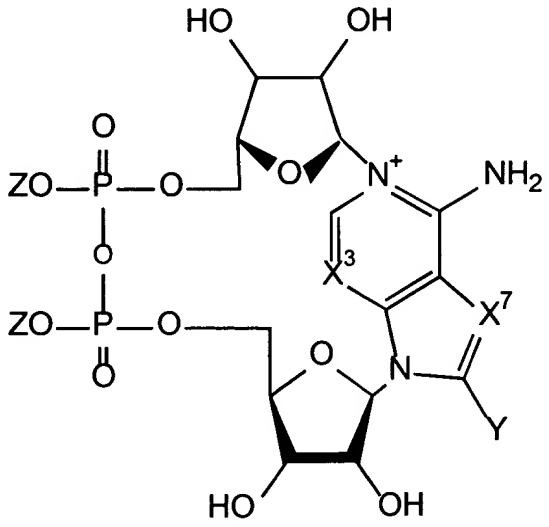
1 (Amended). [Use of] A method for modulating T cell activation *in vivo* or *ex vivo* in a mammal comprising administering to the mammal or a mammalian T cell culture an effective amount of a compound capable of [antagonising] antagonizing a sustained cADPR-mediated rise in intracellular Ca^{2+} levels in a T cell, said rise being in response to stimulation of the T cell receptor/CD3 complex of the T cell[, in the manufacture of a medicament for use in modulating T cell activity].

2 (Amended). [Use] A method according to claim 1 wherein the compound modulates the binding of cADPR to a ryanodine receptor/Ca^{2+} channel.

3 (Amended). [Use] A method according to claim 1 [or claim 2] wherein the compound is a cADPR analogue.

4 (Amended). [Use] A method according to claim 3 wherein the compound comprises an adenine component to which is individually linked two ribose moities or a derivative(s) thereof, which ribose moities are joined *via* a pyrophosphate bridging group.

5 (Amended). [Use] A method according to claim 3 wherein the compound has the formula (2):



(2)

wherein:

X^3 is independently [selected from] either CR^1 [and] or N;

X^7 is independently [selected from] either CR^2 [and] or N;

Y is selected from the group consisting of halo, C_1 to C_{20} hydrocarbyl, $N(R^3)(R^4)$, OR^5, SR^6 nitro and carboxyl;

each of R^1, R^2, R^3, R^4, R^5 and R^6 is independently [selected from] either H [and] or C_1 to C_{20} hydrocarbyl; and

Z is independently selected selected from the group consisting of H, [and] a caging

8 (Amended). [Use] A method according to claim [7] 10 wherein the patient has a graft rejection or an autoimmune disease is selected from thyroiditis, insulitis, multiple sclerosis, iridocyclitis, uveitis, orchitis, hepatitis, Addison's disease, myasthenia gravis, rhematoid arthritis and lupus erythematosus.

15. A compound identified by the method of claim [11, 12 or 13] 17.